Remarks

Claims 1-20 and 28-34 were pending in the subject application. Applicants acknowledge that claim 20 has been withdrawn from further consideration as being drawn to non-elected subject matter. Applicants gratefully acknowledge the Examiner's withdrawal of the rejection under 35 USC §112, second paragraph, and certain of the previous rejections under 35 USC §103. Submitted herewith is a Request for Continued Examination (RCE) under 37 CFR §1.114 for the subject application. By this Amendment, claim 15 has been amended and claim 14 has been cancelled. Support for the amendments can be found throughout the subject specification and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1-13, 15-20, and 28-34 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

Claim 14 is rejected under 35 USC §112, second paragraph, as indefinite. By this Amendment, Applicants have cancelled claim 14, thereby rendering this rejection moot. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §112, second pagragraph is respectfully requested.

Claims 1, 9, 11-19, and 28-34 are rejected under 35 USC §103(a) as obvious over Tang *et al.* (2002) in view of Turgeman *et al.* (2001) and Juan *et al.* (2001). In addition, claim 10 is rejected under 35 USC §103(a) as obvious over Tang *et al.* (2002) in view of Turgeman *et al.* (2001), and Juan *et al.* (2001), and further in view of Nicklin *et al.* (2002). The Examiner acknowledges that the Tang *et al.* reference does not teach a genetically modified stem cell or a nucleic acid sequence encoding a therapeutic product as recited in claim 1 of the subject application or a modified mammalian tissue as recited in claims 28-33. However, the Examiner relies on the Turgeman *et al.* reference for teaching genetically modified stem cells to express desired therapeutic proteins. The Juan *et al.* reference is relied on for teaching an HO-1 gene from adenoviral vector for therapeutic purposes. The Examiner concludes that it would have been obvious to combine the teachings of the cited references to arrive at Applicants' claimed invention. Applicants respectfully traverse these grounds for rejection.

Applicants respectfully assert that the cited references, whether taken alone or in combination, do not teach or suggest the claimed invention.

In responding to Applicants' arguments submitted in the Amendment dated May 4, 2009, the Examiner asserts that Applicants' arguments were directed to "intended use" of a product and that intended use is not entitled to any patentable weight. Applicants respectfully assert that their comments were directed to the uses of the products and methods of the cited references and that these uses are relevant as to why a person of ordinary skill in the art would not have looked to combine the cited references and, thus, do not render Applicants' claimed invention obvious. For example, Applicants noted that the Tang *et al.* reference does not teach or suggest the use of stem or progenitor cells, and more particularly, does not teach or suggest the use of cells autologous to the tissue. Moreover, the vector described in the Tang *et al.* reference was designed specifically for injection directly into heart tissue and not for use in stem cells. Thus, a person of ordinary skill in the art would not look to incorporate the vector of the Tang *et al.* reference into a stem cell or progenitor cell. The secondary references cited by the Examiner under these rejections also do not provide any motivation to genetically modify a stem or progenitor cell with a first and second polynucleotide having the elements as recited in the claims.

Applicants respectfully maintain that the combination of a gene switch/biosensor and a gene amplification system in a stem cell or a progenitor cell is novel and not obvious over the teachings of the cited references. Applicants' claimed invention advantageously provides for cell therapy wherein a patient can have their own stem or progenitor cells prepared from their own tissue (*e.g.*, bone marrow) and then the cells can be provided with a vector (*e.g.*, hypoxia gene switch/transgene) outside the body before injecting the modified cells directly into the target tissue (*e.g.*, heart) of the patient. The claimed invention provides cells, such as adult stem cells derived from bone marrow, a novel and surprising means of surviving in a hostile environment (such as in an injured heart where oxygen levels are very low). It was not obvious to provide cells with means for surviving in the hostile environment because the high rate of death of implanted stem cells was not known in the art at the time of the present invention. When bone marrow stem cells are transplanted into ischemic hearts, the majority of the engrafted cells (over 90%) die within 1-2 days. It is only the present invention that solved the problem of poor cell survival that occurs in stem cell therapy. None of the

cited references teach or suggest anything of relevance in regard to the problem of implanted stem cell survival and, thus, a person of ordinary skill in the art would not have been motivated to combine the exogenous first and second polynucleotide of the subject invention into a stem cell or a progenitor cell. In order to establish a *prima facie* case of obviousness, there must be some suggestion or motivation for combining the references. *In re Geiger*, 2 USPQ2d 1276 (Fed. Cir. 1987). The fact that the high rate of death of implanted stem cells was not known in the art at the time of the subject invention is evidence as to the nonobviousness of the claimed invention.

The Tang *et al.* reference describes testing different types of gene switches, including single vector and double vector models. The rat myoblast cell line H9c2 referred to in the Tang *et al.* reference was only used for testing the vector. It was not used for stem cell transplantation. Nowhere in the Tang *et al.* reference did the authors teach or suggest an approach for improving stem cell survival in therapy. The work reported in the Tang *et al.* reference is directed solely to development of an injectable gene switch which would reside in specific body tissue, such as heart ventricle, defined by the promoter incorporated into the gene switch. Thus, a person of ordinary skill in the art would not have looked to the Tang *et al.* reference for teachings relevant to the preparation of Applicants' claimed invention.

Moreover, Applicants respectfully maintain that the cited references do not teach or suggest a mammalian tissue comprising a genetically modified mammalian stem or progenitor cell as claimed in new claims 28-34. There is no teaching or suggestion in any of the cited references to provide mammalian tissue with a genetically modified stem cell or progenitor cell of the invention. As noted above, the Tang *et al.* reference is concerned with direct gene therapy and not with cell therapy. Thus, Tang *et al.* is only relevant with regard to transforming cells within a tissue with a nucleic acid vector. As noted previously, the intended use of the genetically modified stem cell or progenitor cell is discussed to point out why a person of ordinary skill in the art would not look to the teachings of the cited references, *i.e.*, because they are directed to uses that are not relevant to the claimed invention. It was only the inventors of the claimed invention that realized the problem to be solved and did so by invention of the claimed genetically modified stem cell or progenitor cell and mammalian tissue.

Applicants maintain that the secondary references, Juan *et al.*, Nicklin *et al.*, and Turgeman *et al.*, cited under the §103 rejections fail to cure or overcome the deficiencies of Tang *et al.*, the primary reference. The Juan *et al.* reference is irrelevant as it does not teach or suggest that heme oxygenase 1 is cell protective against apoptosis. Thus, an ordinarily skilled artisan would not have looked to use a polynucleotide encoding heme oxygenase 1 in a genetically modified stem or progenitor cell of the claimed invention.

As the Examiner is aware, in order to support a *prima facie* case of obviousness, a person of ordinary skill in the art must generally find both the suggestion of the claimed invention, and a reasonable expectation of success in making that invention, solely in light of the teachings of the prior art and from the general knowledge in the art. *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). One finds neither the suggestion, nor the reasonable expectation of success, of Applicants' claimed invention in the cited references. Accordingly, reconsideration and withdrawal of the rejections under 35 USC §103(a) is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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Attachment: Request for Continued Examination